In the Claims

This listing of claims will replace all prior versions, and listing, of claims in the application.

Claims 1-25 (canceled)

Claim 26 (currently amended): A method of amplifying a segment of a human β_2-adrenergic receptor gene of a subject wherein the segment comprises sequences encoding the residue glycine 16 comprising the step of[[:

a)]] amplifying [[a]] the segment of the human β_2-adrenergic receptor gene from nucleic acid contained within a ~~biological~~ sample by employing an oligonucleotide primer pair ~~of claim 11~~ wherein at least one primer of said pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof, a primer-dependent DNA polymerase, and a sufficient amount of deoxyribonucleotides to generate a plurality of segments of the gene.

Claim 27 (currently amended): A method for identifying a glycine 16 genetic variation in a human β_2-adrenergic receptor gene of a subject, wherein the glycine 16 genetic variation is associated with disease comprising the steps of:

a) amplifying a segment of the human β_2-adrenergic receptor gene from nucleic acid contained within a ~~biological~~ sample by employing an oligonucleotide primer pair ~~of claim 11~~ wherein at least one primer of said pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof, a primer-

dependent DNA polymerase, and a sufficient amount of deoxyribonucleotides to generate a plurality of segments of the gene; and

b) identifying ~~a sequence~~ a glycine 16 genetic variation [[of]] if present in the resulting amplified products relative to a control using at least one sequence analytical step.

Claim 28 (currently amended): [[A]] The method ~~for identifying a genetic variation in a human β_2-adrenergic receptor gene of a subject according to~~ of claim 27, wherein the sequence analytical step is selected from the group of nucleotide sequencing, single-strand conformation polymorphism assay, allele-specific oligonucleotide hybridization, Southern blot analysis, and restriction endonuclease digestion.

Claim 29 (currently amended): A method for diagnosing a disease associated with a glycine 16 genetic alteration of a human β_2-adrenergic receptor gene of a subject, comprising the steps of:

a) amplifying a segment of the human β_2-adrenergic receptor gene encoding said receptor from nucleic acid contained within a ~~biological~~ sample by employing an oligonucleotide primer pair ~~of claim 11~~ wherein at least one primer of said pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof, a primer-dependent DNA polymerase, and a sufficient amount of deoxyribonucleotides to generate a plurality of amplified segments of the gene;

b) identifying ~~a sequence~~ a glycine 16 genetic variation [[of]] if present in the resulting amplified products relative to a control using at least one sequence analytical step, wherein the glycine 16 genetic variation is associated with asthma or hypertension; and

c) optionally determining a correlation of [[the]] any detected glycine 16 genetic variation between the subject and a control.

Claim 30 (Currently amended): [[A]] The method ~~for diagnosing a disease associated with a genetic alteration of a human β_2-adrenergic receptor gene of a subject~~ of claim 29, wherein the sequence analytical step is selected from the group of nucleotide sequencing, single-strand conformation polymorphism assay, allele-specific oligonucleotide hybridization, Southern blot analysis, and restriction endonuclease digestion.

Claims 31-36 (canceled)

Claim 37 (currently amended): The ~~oligonucleotide primer pair~~ method of claim [[1]] 26 wherein said ~~linear~~ sequence is at least about 18-23 nucleotides in length.

Claim 38 (currently amended): The ~~oligonucleotide primer pair~~ method of claim [[11]] 27 wherein said ~~linear~~ sequence is at least about 18-23 nucleotides in length.

Claim 39 (new): The method of claim 26 wherein each individual primer of said primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 40 (new): The method of claim 26 wherein the primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 41 (new): The method of claim 26 wherein the primer pair comprises SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 42 (new): The method of claim 27 wherein each individual primer of said primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ

ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 43 (new): The method of claim 27 wherein the primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 44 (new): The method of claim 27 wherein the primer pair comprises SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 45 (new): The method of claim 27 wherein the presence of glycine 16 genetic variation is associated with asthma.

Claim 46 (new): The method of claim 27 wherein the presence of glycine 16 genetic variation is associated with hypertension.

Claim 47 (new): The method of claim 29, wherein the glycine 16 genetic variation is associated with asthma.

Claim 48 (new): The method of claim 29 wherein the glycine 16 genetic variation is associated with hypertension.

Claim 49: (new) The method of claim 29 wherein each individual primer of said primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 50 (new): The method of claim 29 wherein the primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 51 (new): The method of claim 29 wherein the primer pair comprises SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 52 (new): The method of claim 29 wherein the sequence analytical step is selected from the group of nucleotide sequencing, single-strand conformation polymorphism assay, allele-specific oligonucleotide hybridization, Southern blot analysis, and restriction endonuclease digestion.

Claim 53 (new): The method of claim 29 wherein said sequence is at least about 18-23 nucleotides in length.

Claim 54 (new): A method of amplifying a segment of a human β_2-adrenergic receptor gene of a subject wherein the segment comprises sequences encoding the residue glycine 16 comprising the step of contacting the segment of the human β_2-adrenergic receptor gene from nucleic acid contained within a sample with an oligonucleotide primer pair wherein at least one primer of said pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof, a primer-dependent DNA polymerase, and a sufficient amount of deoxyribonucleotides to generate a plurality of segments of the gene under conditions suitable for amplification.

Claim 55 (new): The method of claim 54 wherein each individual primer of said primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ

ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, or a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 56 (new): The method of claim 54 wherein the primer pair comprises a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and a sequence that hybridizes under high stringency to the polynucleotide shown in SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 57 (new): The method of claim 54 wherein the primer pair comprises SEQ ID No:5, 5'GAATGAGGCTTCCAGGCGTC3', or a complement thereof, and SEQ ID No:6, 5'GATGATGCCTAACGTCTTG3', or a complement thereof.

Claim 58 (new): The method of claim 54 wherein said sequence is at least about 18-23 nucleotides in length.

REMARKS/ARGUMENTS

Claims 1-38 were pending in the present application. By virtue of this response, claims 1-25 and 31-36 have been cancelled, without prejudice or disclaimer; claims 26, 27, 28, 29, 30, 37 and 38 have been amended; and new claims 39-58 have been added. Accordingly, claims 26-30, 37-38 and 39-58 are currently under consideration. Support for the amendments to claims 26, 27 and 29 and new claims 39-44 and 49-51 and 54-57 regarding primers can be found at least at page 19, lines 4-12; page 29, under Example 2 and in Figure 2. Support for the amendments to claims 26, 27 and 29 and new claims 45-48 regarding the glycine 16 genetic variation can be found throughout the specification and in particular at page 27, lines 15-22.

Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any subject matter of the claims as previously presented or an acquiescence of any rejection and/or objection levied by the USPTO. Applicants reserve the right to prosecute any cancelled subject matter in a related application.

Concerning Rejections Under 35 U.S. C. 112, first paragraph

A. Claims 1-6, 11-16, 21-38 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The Examiner also alleges that the current claims do not provide descriptive support for diseases other than asthma or hypertension.

Applicants traverse this rejection of claims. The written description guidelines (see Federal Register: January 5, 2001) state that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed and that rejection of an original claim for lack of written description should be rare. The relevant question is whether there is sufficient written description to inform a skilled artisan that Applicants were in possession of the claimed invention as a whole at the time the application was filed. One of skill in the art would

recognize that Applicants were in possession of the claimed invention. Therefore, the claims are in compliance with Section 112, first paragraph written description requirements.

The Examiner states at page 2 of the Office Action that the claims encompass a genus of nucleic acids which are different from those disclosed in the specification. Applicants disagree. The claims as originally filed and currently pending are described in the specification across their full scope. At page 3 of the Office Action, the Examiner states that claims have no structural limitation or requirement. Applicants disagree and point out that SEQ ID NOs: are recited in every claim. In an effort to expedite prosecution, Claims 1-6, 11-16, and 21-25 have been cancelled, without prejudice, thereby mooting their rejection. Applicants wish to direct the Examiner's attention to the Office Action page 3, second paragraph where the Examiner states: "the specification only discloses association of nocturnal asthma or essential hypertension with the specific glycine 16 polymorphism in the human *alpha-1B* adrenergic receptor gene." The Examiner's characterization of glycine 16 polymorphism in the alpha-1B adrenergic receptor gene is referenced throughout the Office Action. This may reflect a misunderstanding on the part of the Examiner as to the glycine 16 polymorphism. The specification at page 3, lines 7-24 discloses that the glycine 16 genetic variation of the human β_2 adrenergic receptor is associated with asthma and hypertension.

Amended claim 26 recites a method of amplifying a segment of a human β_2-adrenergic receptor gene of a subject wherein the segment comprises sequences encoding the residue glycine 16 and further recites primer sequences. There is specific written description for this amendment to claim 26 throughout the specification and in particular at page 19, lines 4-12; and page 22, lines 15-24. Amended claim 27 recites a method for identifying a glycine 16 genetic variation in a human β_2-adrenergic receptor gene of a subject, wherein the glycine 16 variation is associated with disease and further recites primer sequences. There is specific written description for this amendment to claim 27 throughout the specification and in particular at page 19, lines 4-18. There is specific written description support for the association of asthma and hypertension with glycine 16 which can be found at least at page 27, lines 15-22. Amended claim 29 recites a method for diagnosing a disease associated with the glycine 16 genetic alteration of a human β_2-adrenergic receptor gene of a

subject wherein the glycine 16 variation is associated with asthma and hypertension, and further recites primer sequences. There is specific written description for the amendment to claim 29 through out the specification and at least at page 27, lines 15-22 and in Example 2 at page 29. Applicants believe that the amendment to claims and new claims are in full compliance with the written description requirement of Section 112, first paragraph.

B. Claims 24, 25, 29-31, 33 and 34 stand rejected under 35 U.S.C 112, first paragraph, allegedly because the specification, while being enabling for diagnosis of nocturnal asthma and essential hypertension by association with the glycine 16 polymorphism, does not reasonably provide enablement for diagnosis of any other disease or the particular diseases with other polymorphisms. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants traverse this rejection of claims. The Examiner alleges at page 6 of the Office Action that no specific sequences are recited for the alpha-1B adrenergic receptor gene. Claim 1 as amended in Applicants Amendment under 37 C.F.R. 1.111 mailed March 5, 2003, relates to the α_{1B} adrenergic receptor gene and recites SEQ ID NO:9 (which is disclosed in Figure 1). The Examiner at page 6 of the Office Action states that the quantity of experimentation is large. M.P.E.P 2164.06 states that an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. The Examiner alleges that there is only one working example. While several working examples are disclosed in the specification, Section 112, first paragraph, does not require that any working examples be present in the specification. The specification provides disclosure on how to make and use the primer pairs; disclosure on how to amplify the α_{1B}- and β_2-adrenergic receptor genes and disclosure on how to use the primer pairs for the diagnosis of disease. See for example the specification at page 22, lines 15-24, and at page 32, and Example 6 which provides a working example of diagnosis of disease associated with genetic variations. One of skill in the art would be able to make and use the claimed invention without undue experimentation.

Applicants believe that the claims as filed in the Amendment under 37 C.F.R. 1.111 mailed March 5, 2003 are in compliance with Section 112, first paragraph. While not acquiescing to the

Examiner's rejections, in an effort to expedite prosecution, Applicants have cancelled claims 21-25, without prejudice, thereby mooting their rejection. In an effort to expedite prosecution, Applicants have amended claims 26, 27 and 29, and claims dependent thereon, and have added new claim 39-56. Claims 26 and 53 recite methods of amplifying a segment of a human β_2- adrenergic receptor gene of a subject wherein the segment comprises residues encoding the residue glycine 16. Claim 27 recites a method for identifying a glycine 16 genetic variation in a human β_2- adrenergic receptor gene of a subject wherein the presence of the glycine 16 is associated with diseases. Claim 29 recites a method for diagnosing disease associated with glycine 16 genetic alterations and recites that the disease associated with glycine 16 genetic variation is asthma or hypertension. The Examiner states at page 5 of the Office Action under paragraph 3 that the specification is enabling for diagnosis of asthma and hypertension by association with the glycine 16 polymorphism. One of skill in the art following the teachings of the specification would be able to make and use the claimed invention without undue experimentation.

Applicants disagree with the Examiner's allegation that the specification does not provide enablement for diagnosis of any other diseases or the particular diseases with any other polymorphism. In particular, Applicants bring to the Examiner's attention Buscher et al., 2002, Pharmacogenetics 12(5):347-353, submitted to the USPTO in the Information Disclosure Statement mailed March 5, 2003, which disclose that the arginine to glycine 16 genetic variation and the threonine to isoleucine 164 genetic variation in the β2 adrenergic receptor gene are associated with cystic fibrosis. Regarding the reference to Buscher et al., the Examiner states that publications dated after the filing date cannot be used to show what was known at the time of the filing. The requirement of adequate enabling disclosure as of the filing date does not prohibit Applicants from submitting additional evidence in support of enablement during prosecution which necessarily occurs after an application has been filed. Furthermore, the requirement that enablement be judged as of the filing date does not preclude claims from encompassing later-developed subject matter not even contemplated by applicants at the time they filed the patent application. While Applicants disagree with the Examiner's allegation that the specification does not provide enablement for diagnosis of any other diseases or the particular diseases with any other polymorphism, in an effort

to expedite prosecution, Applicants have amended claims to recite glycine 16 and the specific diseases asthma and hypertension.

Applicants submit that the claims are in compliance with Section 112, first paragraph and request withdrawal of the Section 112, first paragraph rejection of claims.

Concerning the Rejection Under 35 U.S.C. 112, second paragraph

Applicants acknowledge the withdrawal of the rejection under 35 U.S.C., second paragraph in view of the Amendment filed March 5, 2003.

Concerning the Rejection Under 35 U.S.C. 102(b)

Claims 1 and 2 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Synaptic Pharmaceutical Corporation (WO 94/08040).

Applicants traverse this rejection of claims. Applicants have canceled claims 1 and 2, without prejudice, thereby mooting their rejection. Applicants request withdrawal of this rejection of claims.

Concerning Rejections Under 35 U.S.C. 103(a)

A. Claims 1-14, 16-20, 21-37 and 38 stand rejected under 35 U.S.C. 103(a) as allegedly obvious over Synaptic Pharmaceutical Corporation (WO 94/08040) in view of Ramarao et al. (J. Biol. Chem. (1992) 267(30):21936-21945) and further in view of Emorine et al. (Proc. Natl. Acad. Sci. (1987) 84:6995-6999).

Applicants traverse this rejection of claims. Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings.

Applicants submit that there is no motivation to combine references and, even if combined, the combination of references does not produce the claimed invention. While Applicants disagree with this rejection, in an effort to expedite prosecution, Applicants have canceled claims 1-14, 16-20, and 21-25, without prejudice, thereby mooting their rejection. Claims 26-30 which have been amended, and new claims 39-58 relate to the β_2 adrenergic receptor gene.

Applicants respectfully point out that WO 94/08040 relates to alpha 1 adrenergic receptors and has no disclosure whatsoever regarding β_2 adrenergic receptors. Ramarao et al. relate to human $alpha_{1B}$ adrenergic receptor and have no disclosure whatsoever regarding β_2 adrenergic receptors. Emorine et al. disclose the structure of the gene for human β_2-adrenergic receptor and have no teachings or suggestions whatsoever regarding identifying polymorphisms in the β_2- adrenergic receptor gene by using primers, much less the presently claimed primer pairs. Furthermore, there is no suggestion in Emorine et al. of the association of the glycine 16 with any disease. The presently claimed invention is non-obvious in view of the art cited by the Examiner.

B. Claims 1, 2, 11, 12 and 21-38 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Synaptic Pharmaceutical Corporation (WO 94/08040) in view of Cotton et al. (Current Opinion in Biotechnol (1992) 3:24-30).

Applicants traverse this rejection of claims. To expedite prosecution, claims 1-2, 11-12, 21-25, and 31-36 have been canceled without prejudice thereby mooting their rejection. Claims 26-30 have been amended and recite the β_2-adrenergic receptor gene. WO 94/08040 has no disclosure whatsoever regarding β_2-adrenergic receptor. Cotton et al., which generally relate to detection of mutants in DNA, have no teachings whatsoever regarding the β_2-adrenergic receptor gene. Cotton et al. does not cure the deficiencies of the WO 94/08040. The presently claimed invention is non-obvious over the cited art. Applicants respectfully request withdrawal of the Section 103(a) rejection of claims.

CONCLUSION

Applicants have made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action and believe that the present amendment places the claims in condition for allowance. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 220002058901.

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Respectfully submitted,

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